after selecting CD4+ cells that are HIV- and prior to expanding the selected cells, growing a plurality of aliquots in the presence of mitogenic agents;

selecting from the aliquots those that are HIV-; and

then expanding the selected cells to an excess of 1 x 10^{10} cells per liter.

39. (Twice Amended) The method of claim 37, wherein the cells are activated with anti-CD3 monoclonal antibodies in the presence of interferon-γ (IFN-γ).

154. (Amended) The method of claim 40, wherein cell expansion is effected in a hollow fiber bioreactor.

REMARKS

A check for the fees for filing a CPA, an IDS and for a five month extension of time accompanies this response. Any fees that may be due in connection with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 37-40 and 154, 160, 161, 163-177 are presently pending. Claims 36, 155, 156, 157, 158, 159 and 162 are cancelled herein without prejudice as being withdrawn from consideration as allegedly drawn to non-elected subject matter. Previously withdrawn claims 38, 40, 154, 163, 164 and 166 are now dependent upon previously elected claims 37 and 39, and thus remain presently pending. Applicant reserves the right to file divisional applications to the withdrawn subject matter; the Office is reminded that as between any of the cancelled claims and the presently pending claims obviousness-type double patenting cannot be held. Claims 168-177, which encompass elected subject matter are added.

The amendment to claims 37 and 38 to reflect in excess of 10^{10} cells/liter finds basis in previous claims 155, 159 and 162, which have been cancelled

herein. These also find basis throughout the original parent application, see, *e.g.*, original claim 14 therein; see, also, original Example 2 (Example 3 in the instant application).

Claims 168 and 169, which are added herein, cover subject matter in the presently pending claims, and find exact basis in the parent application in claims 1, 12 and 14 and in Example 2 therein (see, *e.g.*, lines 4-6 for claim 168; and lines 13-24; see also Example 3 in the instant application). Basis is also found throughout the parent application that states that the goal is to grow the cells to densities of 10^8 cells ml (see, *e.g.*, page 14, line 14), page 14, lines 15-16 which state that "only one liter of culture volume is required to generate 1 x 10^{11} cells."

A marked up copy of claims showing the amendments herein is appended hereto.

INFORMATION DISCLOSURE STATEMENT

A further Information Disclosure Statement is filed with the Request for filing CPA.

THE PRIORITY DATE

Regarding the priority date for the claimed subject, although Applicant maintains that the instantly claimed subject matter finds basis in the parent application. The methods and products described in the parent application are the same as the methods described in the instant application. The instant application **updates** terminology, which is permissible without a loss of priority date. Moreover, the issue regarding terminology is moot since the pending claims, amended to conform to the election of species, do not employ the terminology. A Th1 cell is a Th1 cell in the parent application and in the instant application. Whether it part of a broad genus called effector cells in the parent application or are part of the subgenus regulatory cells, which were encompassed within the genus effector cells in the parent application is

irrelevant. A Th1 cell refers to the same Th1 cell as it did in the parent application.

Any skilled artisan would find basis for the presently pending claims in the parent application. The same Example that exemplifies this subject matter is in the parent application and the intent and disclosure of the parent application is to provide high density compositions of Th1 or Th2 or other such cells and use them for altering immune balance. This disclosure is in both applications. In addition both applications describe the claimed method of preparing HIV-purged cells.

Relevant law

The purpose behind written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in

the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Furthermore, the **subject matter of the claim need not be described literally (i.e., using the same terms or inhaec verba)** in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. This conclusion will result in the rejection of the claims affected under 35 U.S.C.112, first paragraph - description requirement, or denial of the benefit of the filing date of a previously filed application, as appropriate.

The guideline promulgated by the U.S. PTO embody these rules:

> In rejecting a claim, set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should:

(1) identify the claim limitation not described; and

(2) provide reasons why a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

in this instance, there is not basis to conclude that a person skilled in the art at the time the application was filed would not have recognized the description of this limitation in view of the disclosure of the application as filed.

Analysis

Both applications are directed to the concept of treating diseases by altering or restoring immune balance by preparing large numbers of one type of cell, particularly at high density (see, *e.g.*, page 14, lines 14-16 which state that "only one liter of culture volume is required to generate 1 x 10^{11} cells" in the parent application and the original claims in the instant application; see, also, page 17, lines 6-11 which describe obtaining densities greater than 10^8 cells/ml; Example 2, directed to expansion of the HIV- cells refers back to the earlier examples for the methods for producing the greater than 10^{10} cells that were produced at density of about 10^8 cells), and administering the compositions to a mammal to restore or alter (depending upon the treatment) the immune balance by administering such compositions. The compositions contain either cells that are predominantly of a type that has one cytokine profile (i.e., what called Th1 or Th1-like cells) or another cytokine profile (i.e. Th2 or Th2-like cells). Also methods involve a step of collecting cells from a mammal and then treating them so that cells with a particular cytokine profile predominate. In addition, the application provides methods for producing high densities of such cells.

It is not necessary that priority application describe in *ipsis verbis* the claim in the application. The priority application must reasonably convey to those skill in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him (*In re Edwards*, 558 F.2d

1349, 196 USPQ 465 (CCPA 1978); *In re Driscoll*, 562 F.2d 1245, 195 USPQ 434 (CCPA 197).

In the parent application, U.S. provisional application Serial No. 60/044,693 (converted to a provisional from application Serial No. 08/506,608) claim 1 recites:

1. A method for generating autologous effector immune cells, the method comprising:

collecting leukocyte containing material from a mammal; and
exposing the leukocyte containing material to mitogenic monoclonal antibodies to induce *in vitro* cell proliferation sufficient for infusion into the mammal for use in an immunotherapy treatment, wherein the *in vitro* cell proliferation is produced without the use of exogenous interleukin-2.

Claim 15 recites that cells are produced by first treating them to alter their cytokine production profile; and are then proliferation to numbers sufficient for infusion into a mammal for use in the adoptive immunotherapy.

Claims 11 recites that the leukocyte containing material is treated with mon or more cell-surface protein specific monoclonal antibodies; claims 7-10 and 17-23 recite that the cells are treated to become Th1 or Th2 cells

Claims 14 and 27 of that case recites that the cells are proliferated to "an excess of 1 x 10^{10} cells."

Claim 7 recites that the cells are Th1-like or Th2-like cells, thereby indicating that as originally filed, what are now called regulatory cells were contemplated to be within the scope of the original claims and to be separately claimed.

The parent application is directed to methods for the production of high concentrations and amounts of homogeneous compositions of immune cells, including Th1, Th2, and also LAK, CTL and TIL cells, in the absence of exogenously added IL-2. In the parent application, the term "effector" cell was used to encompass all types of regulatory cells. Dependent claims separated

out the Th1 and Th2 cells from the generic type. Claim 1 generically encompassed all types of T cells.

In the instant application, the nomenclature, **not** the intended scope of the claims, was modified so that the generic language refers to what was called effector cells in the parent application as "immune cells" Compare claim 1 as originally in the instant case with claim 1 of the parent case. The language "effector" is changed to immune cell. Further, two classes of cells were defined: regulatory immune cells, which are clearly defined (as discussed below) to include Th1 and Th2 cells, which can be identified by their distinct cytokine profiles and which act on other cells; and effector immune cells, which are defined as the LAK, CTL, MAK and TIL type cells.

The parent specification states at page 7, line 16,. that effector cells include Th1, Th2-like cells. The parent specification describes Th1 and Th2 cells at page 8, lines 27, page 9, line 3, and page 9, lines 20-24; and states at page 9, lines 25-28:

> *Accordingly, it is desirable to have the ability to produce large quantities of autologous Th1 T-cells in disease states where a Th2 cytokine profile predominates (infectious disease) and Th2 T-cells in a TH1-dominant disease (chronic inflammation and autoimmune disease).* (emphasis added)

Methods for differentiation of immune cells into Th1 or Th2 cells are described at page 11, lines 11-19.

In the parent specification, production of clinically relevant numbers of cells Th1 cells (and also Th2 cells) is described at page 7, lines 6-25. At page 8, lines 25,- page 9, line 3, the parent specification states that CD4+ cells can be subdivided into TH1 cells and Th2 cells. At page 9, line 25, - page 10, line the parent application states that it is desirable to produce large quantities of Th1 T-cells in disease states where a Th2 cytokine profile predominates, such as in infectious diseases, and to produce large quantities of Th1 cells in diseases in which Th1 cells predominate, such as chronic inflammation and autoimmune

disease. The parent application describes large quantities as an "excess of 10^{10} cells (see page 6, line 26, page 7, lines 13-15). At page 10, lines 5-7, the parent application states that:

> The present invention includes a process that enables the production of large quantities of immune cells, such as Th1 and Th2 cells, for use in ACI of human disease.

The process for preparing these cells is described on page 10, line 14, - page 14, line 20). It is exemplified in Example 1, which shows that non-specific $CD4^+$ and $CD8^+$ cells can be expanded to "clinically relevant numbers" (page 30, lines 9-10). Greater than 10^{10} cells $CD4^+$ and $CD8^+$ were shown to be produced. Example 2 (see page 34 of the parent application) shows preparation of clinically relevant numbers of virally purged (HIV-) $CD4^+$ Th1 cells and claims 28 and 29 are directed to virally purged CD4+ cells, and claim 29 recites that the cells are Th1 cells.

In particular, Example 2 describes expansion of HIV- $CD4^+$ cells in the absence of IL-2. Example 2 describes the isolation of $CD4^+$ cells from an HIV patient, activation of the cells with immobilized and CD3 mAB in the presence of IFN-γ, selection for HIV- cells, and then expansion as in Example to produce more than 10^{10} cells. Example 3 shows selection and expansion of CTL cells, in the absence of IL-2, to amounts grater than 10^{10}; and Example 4 shows activation and expansion of HIV- $CD4^+$ cells in the absence of IL-2 to produce greater and 10^{10} Th2 $CD4^+$ cells.

The scope of the claims and subject matter of the claims as originally filed and as filed in the instant cased are the same. The definitions were slightly modified in the instant case; but it is clear from the context that broad claims to the general method of inducing activation and proliferation using mitogenic antibodies in the absence of exogenous IL-2 (see claims 1-14), and claims in which the cells are caused to differentiate into Th1 or Th2 (or Th1-like or Th2-

like) populations of cells prior to proliferation (claims 15-27) cover the same methods.

The parent application states, starting at page 6, line 23, that:

> use of ACI protocols will require technology that enables: the generation of homogeneous populations of immune effector cells [*i.e.*, cells that include TILs, LAKs, CTLs, Th1, Th2 cells]; the consistent growth of effector cells to clinically relevant dosages (*i.e.*, greater than 10^{10} cells) without the use of IL-2; . . . and the ability to reinfuse the cells without the need for systemic infusion of IL-2. Furthermore additional *in vitro* differentiation strategies are need to broaden the types of cells available for ACI protocols.
>
> The present invention addresses each of these requirements, disclosing a method to differentiate Th1 or TH2 cells *in vitro* and grow these cells to clinically relevant numbers without the use of IL-2.

The parent application also makes it abundantly clear that the prior art all disadvantageously (see page 6, line 5, - page 7, line 5):

> include the use of IL-2 as a growth stimulant, requiring Il-2 also to be infused concomitant with the cells . . .. With the exception of the A-LAK protocol, no prior art method attempts to purify the effector cells to generate homogeneous cell populations.. . .
>
> Clinical testing of ACI protocols in cancer has [been] greatly curtailed . . . because the potential efficacy of LAK and TIL therapies has been overshadowed by the substantial toxicity of the treatments. The toxicity is attributed to the administration of systemic IL-2 . . . [that] is necessary in these protocols because lymphocytes differentiated or grown in IL-2 die within 48 hours of IL-2 withdrawal.
>
> Therefore, expanded use of ACI protocols will require technology that enables: the generation of homogeneous populations of effector immune cells; the consistent growth of effector cells to clinically relevant dosages *(i.e., greater than 10^{10}* **cells) without the use of IL-2** . . ..
>
> The present invention addresses each of these requirements disclosing a method to differentiate Th1 or Th2 cells *in vitro* and grow these cells to clinically relevant numbers without the use of IL-2.

This provides clear unequivocal basis for the pending claims in the present application.

The instant application has been rewritten for clarity, not to add new matter to the original claims, and to provide additional examples of applications of the technology. To distinguish between differentiation of cells to produce LAKs, TILs and CTLs, from differentiation to produce Th1, Th2 and Th3 cells and subcategories thereof, different nomenclature has been adopted. The same cells are encompassed by the claim and with respect to those cells the same terminology is used.

All of the instant claims bind basis in the parent application as filed. The parent application is directed to methods for production of clinically relevant numbers (described therein as in excess of 10^{10} cells) at high density (described therein as greater than 10^{8} cells/ml), including methods for production of clinically relevant numbers of CD4+ cells purged of virus (see, *e.g.*, Example 2 in the parent application and the claims).

Finally, as discussed below, whether or not basis in the parent application is accorded to some or all of the instant claims is not relevant to the patentability of the instant claims over the cited art and art of record. None of the cited references, singly or in any combination thereof, teaches or suggests methods for preparation of compositions containing predominantly one type of T-cell, nor methods for expansion of such cells in the absence of IL-2. There is no art of record that teaches or suggests such methods or the resulting compositions.

In particular, with respect to the claims pending in this case, none of the cited references, singly or in any combination thereof, suggests the steps of the claimed methods in which cells are purged of virus and expanded under conditions for production of Th1 cells. This technology has great promise and it is the purpose of the patent laws in the U.S. to promote its progress. The Examiner by applying standards that are not US law, is thwarting this development.

THE REJECTION OF CLAIMS 37, 39, 159-161, 165 and 167 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 37, 39, 159-161, 165 and 167 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled are that the inventor, at the time the application was file, had possession of the claimed subject matter, is respectfully traversed. It is respectfully submitted that this rejection has been rendered moot by the amendments to claims 37 and 39 herewith, whereby the term "isolating" has been replaced with the term "collecting," which are believed to have the same meaning and scope within the context of the claimed methods. It is respectfully submitted that the term "collecting," in the context of collecting mononuclear cells, finds support in the specification, at page 28, line 20 through page 29, line 11, which states:

> **C. Methods for production of regulatory cells**
>
> A method for obtaining regulatory cells for use in ACT protocols is provided herein. A method for obtaining effector cells for use in ACT protocols without the need for exogenous agents, such as IL-2, that sustain the viability of such cells is also provided. The method includes some or all of the following steps: (1) **collecting mononuclear cells** from a patient; (2) treating the cells *ex vivo* with that agents that cause some or all of the cells to the differentiate into desired T cell subtypes; (3) purifying the resulting cells; and (4) expanding these cells by contacting them with a mitogenic agent that specifically interacts with a cell surface receptor. Such agents are herein preferably mitogenic monoclonal antibodies. The expanded cells may be further purified to select for the desired subtype.
>
> **1. *Collecting* mononuclear cells**
>
> Mononuclear cells (*i.e.*, lymphocytes and monocytes) can be obtained from a variety of sources, including, but not limited to, peripheral blood, lymphoid tissue, biopsy tissue or from body cavity lavage procedures. Preferably, the cells are obtained by simple venipuncture (50-500 ml). When larger numbers of cells are required, they may be obtained by a lymphapheresis procedure. The mononuclear cells can be purified from the blood using Ficoll-Hypaque density gradient centrifugation or any other suitable method.

See also, Applicant's specification, at Example 3, section A., which states:

> **A. Obtaining Mononuclear Cells**
> An HIV^+ patient, identified by a routine blood screening procedure confirmed by Western Blot analysis, in WHO stage IV was the donor for this study. The patient underwent a leukopheresis procedure for **collection** of peripheral blood mononuclear cells.

In the Advisory Action, the Examiner indicates that the proposed amendments will not be entered and the final rejection stands because they allegedly raise new issues, raise issues of new matter and are not deemed to place the application in better form for appeal. Regarding the issue of new matter, the Examiner alleges that "[t]here is no support in the specification for the recitation of "collecting mononuclear cells from a patient infected with HIV" in proposed claim 37. The Examiner alleges that the specification, at page 28:

> does not refer to the claimed method (eg. [sic] it refers to a method for production of regulatory cells, not the claimed method of producing virally purged CD4+ cells). Regarding Example 3 in the specification, said example refers to collection of mononuclear cells via leukopheresis. The proposed claim does not recite that the mononuclear cells were collected via leukopheresis.

Regardless of the purpose for collecting the mononuclear cells, it is respectfully submitted that the specification clearly and explicitly provides basis and support for the phrase "collecting mononuclear cells." The entire application (and the parent application) is directed to methods in which mononuclear cells (or leukocyte-containing material) is collected. The Example is not intended to be limiting of such collection procedures, but describes an experiment that was performed. NOWHERE in the application nor the parent application does it state that any method of collection is specific to the type of mammal or patient from which the material is collected. A working example, merely describes on embodiment and what was done in a particular experiment; it does not nor can it be construed to limit the application to only that method of collection.

Moreover, the specification, at page 29, lines 4-11, clearly teaches that:

> Mononuclear cells (*i.e.*, lymphocytes and monocytes) can be obtained from a variety of sources, including, but not limited to, peripheral blood, lymphoid tissue, biopsy tissue or from body cavity lavage procedures. Preferably, the cells are obtained by simple venipuncture (50-500 ml). When larger numbers of cells are required, they may be obtained by a lymphapheresis procedure. The mononuclear cells can be purified from the blood using Ficoll-Hypaque density gradient centrifugation or any other suitable method.

Thus, it is respectfully submitted that the specification explicitly supports the phrase "collecting mononuclear cells." Accordingly, in view of the amendments to claims 37 and 39, reconsideration and withdrawal of this rejection is respectfully requested.

In the Advisory Action, the Examiner alleges that the amendments to claim 37 would require a new rejection over 35 U.S.C. 112 second paragraph in that proposed claim 37 recites "in excess of 1 x 10^{10} cells per liter", while claim 160 recites "in a volume of 500 mls or less" and therefore claim 160 would lack antecedent basis in proposed claim 37. Contrary to the Examiner's assertion, the only term in claim 160 that should require antecedent basis is "the cells", which clearly has antecedent basis in claim 37. It is respectfully submitted that the phrase "to an excess of 1 x 10^{10} cells per liter" in newly amended claim 37 clearly encompasses the phrase "to an excess of 1 x 10^{10} cells in a volume of 500 mls or less." Accordingly, reconsideration and withdrawal of this proposed rejection is respectfully requested.

THE REJECTION OF CLAIMS 37, 39, 159-161, 165 and 167 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 37, 39, 159-161, 165 and 167 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled are that the inventor, at the time the application was file, had possession of the claimed subject matter, is respectfully traversed. The Examiner urges

that there is no "support in the specification for recitation of "mitogenic antibodies" in claims 36 and 37.

It is respectfully submitted that there is indeed basis in this application and in the parent application for the phrase "mitogenic antibodies." Attention is directed, for example, to Applicant's specification, at page 18, lines 10-16, which states:

> Suitable **mitogenic antibodies** may be identified empirically by testing selected antibodies singly or in combination for the ability to increase numbers of a specific effector cell. Suitable **mitogenic antibodies** or combinations thereof will increase the number of cells in a selected time period, typically 1 to 10 days, by at least about 50%, preferably about 100% and more preferably 150-200% or more, compared to the numbers of cells in the absence of the antibody.

Thus, the Examiner's assertion regarding written description, at p. 3, lines 11-12 of the Official Action, that "[t]here is no support in the specification for the recitation of 'mitogenic antibodies' in claim 37" **is not correct.** Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

THE REJECTION OF CLAIMS 37 AND 39 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 37 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being dependent on claim 36, which the Examiner alleges is "non-elected." This rejection has been rendered moot by the amendments to claims 37 and 39 herewith, such that they no longer depend from claim 36. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

THE REJECTION OF CLAIMS 37, 39, 159-161, 165, 167 UNDER 35 U.S.C. § 103(a)

Claims 37, 39 and 159-161

Claims 37, 39 and 159-161 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over O'Garra *et al.* (1994) *Current Opinion in Immun. 6*:458-466 in view June *et al.* (International PCT application No. WO 94/29436) or June *et al.* (U.S. Patent No. 5,858,358) and Carew (U.S. Patent No.

5,123,901) and Nabel *et al.* (1987) *Nature 326*:711-71 because O'Garra *et al.* is alleged to teach that Th1 cells can be produced, June *et al.* (PCT or US Patent) teaches methods of expanding T cells; Nabel teaches that cell activation results in production of HIV virus in latently infected T cells, and Carew teaches that HIV^+ cells can be removed from blood by treatment with immunoreactive beads coated with an HIV-binding reagent. The Examiner concludes that the ordinarily skilled artisan would have "prepared cells at any desired concentration" and to have "created the claimed invention" because O'Garra *et al.* teaches that Th1 cells can be produced, June *et al.* teaches methods of expanding cells, Carew teaches that HIV^+ cells can be removed from blood. The Examiner states that June *et al.* provides motivation because June *et al.* teaches "a variety of uses for expanded T cell subsets" and Carew teaches that "HIV infected T cells should be removed from blood product."

This rejection is respectfully traversed.

As discussed below, June *et al.* does not teach or suggest preparation of Th1 cells at any concentration for any purpose and does not suggest preparation of cells at densities of greater than 10^8 cells/ml; O'Garra *et al.* merely teaches that Th1 cells exist, and Nabel and Carew cure none of these defects.

The Claims

Claim 37 is directed to a method of producing virally purged CD4+ Th1 cells by collecting mononuclear cells from a patient infected with HIV, activating the cells by contacting the cells with mitogenic antibodies, selecting CD4+ cells that are HIV- after activation, and then expanding the selected cells to clinically relevant numbers in excess of 10^{10} in the absence of interleukin-2 (IL-2). The cells are expanded under conditions that produce Th1 cells.

Claim 38 now depends on 37 and is directed to the method where after the selecting step and prior to expanding the selected cells, a plurality of aliquots of the cells are grown in the presence of mitogenic agents, and HIV- cells are selected and then expanded. Claim 39 and 40 specify the reagents

used to activate and grow the cells. Claims 154 and 165-167 recite that the cells are expanded in a hollow fiber bioreactor, and claims 160-161 and 163 and 164 recite the density of cells.

Claim 168 is directed to a method of expanding virally purged CD4+ cells in the absence of IL-2 and to amounts in excess of 10^{10} cells at a density of at least about 10^8 cells/ml. Claim 169 specifies that the cells are expanded under conditions that lead to Th1 cell production.

Teachings of the cited references and differences from the instant claims

O'Garra *et al.*

O'Garra *et al.* is directed to a study to assess the role of cytokines in determining T-lymphocyte function. O'Garra *et al.* teaches that encounter with a host antigen can result in either cell-mediated or humoral classes of immune response and that these responses are attributable to the heterogeneity of $CD4^+$ T cells. O'Garra *et al.* further teaches that mouse $CD4^+$ T cell clones can be divided into two predominant cytokine secretion profiles designated Th1, which refers to cells that produce IL-2 and IFN-γ and other factors that promote delayed-type hypersensitivity reactions, and Th2, which refers to cells that produce Il-4, Il-5 and IL-10. The subsets by virtue of the differing cytokine profiles cross-regulate immune responses.

O'Garra presents the results of studies designed to elucidate the pathways by which each type of subset is induced. O'Garra *et al.* concludes (page 462):

> . . . The question of whether Th1 and Th2 cells all arise from a common precursor, possibly a Th0-type cell, and whether such populations are malleable or can be differentiated further, remains ***an unresolved issue***, with important implications for the treatment of chronic disease. (emphasis added)

Thus, O'Garra *et al.* elucidates *in vivo* pathways responsible for development of a Th1 or Th2 response *in vivo*. O'Garra *et al.* does not teach or suggest production of such cells *in vitro* nor any conditions that promote Th1 cell

differentiation to produce a population of cells that contains predominantly Th1 cells, as required by the instant claims.

O'Garra *et al.* merely speculates (page 459, col. 1) that the ability to control the emerging Th cell phenotype *in vivo* following exposure to antigen offers the potential to induce a response ***in vivo*** appropriate for each pathogen. O'Garra *et al.* does not suggest any *in vitro* methods for induction of such responses nor the use in immunotherapy protocols. O'Garra *et al.* does not teach or suggest any method for producing virally purged CD4+ Th1 cells and certainly not an *in vitro* or *ex vivo* method nor a method performed in the absence of Il-2.

O'Garra *et al.* concludes that it is not clear whether Th1 and Th2 phenotypes can be altered. Thus, O'Garra *et al.* does not teach or suggest a method for production of compositions of Th1 cells, particularly a method for virally purging any cells nor for production of compositions of virally purged CD+4 Th1 cells *in vitro*, nor does O'Garra *et al.* provide any motivation to produce large numbers or high densities of "virally purged" cells of any type.

O'Garra *et al.* does not teach a method involving collecting mononuclear cells from a patient infected with HIV, activating the cells by contacting the cells with mitogenic antibodies, selecting CD4+ cells that are HIV- after activation, and then expanding the selected cells to clinically relevant numbers in excess of 10^{10} in the absence of interleukin-2 (IL-2). Further O'Garra *et al.* does not suggest directing differentiation of the cells during activation to produce Th1 cells.

Therefore, O'Garra is deficient in failing to teach or suggest any steps in the instantly claimed methods.

June *et al.* (WO 94/29436 or U.S. Patent No. 5,858,358)

The disclosures of these two references appear to be substantially identical and are addressed together. The Examiner alleges, at page 5, lines 8-12 of the Official Action, that:

> June *et al.* (WO 94/29436)(Figures 1 and 2, pages 4-35) or June *et al.* (US Patent 5,858,358)(Figures 1 and 2, columns 4-32) both teach methods of expanding T cells to clinically relevant numbers without using exogenous growth factors (see abstract). Figures 1 and 2 of said publications show expansion of T cells to greater than 10^{10} cells.

June *et al.* does not teach growth of T cells to amounts exceeding 10^{10} cells and in a volume of a liter or less as required by the instant claims.

The data shown in Figures 1-3 of June *et al.* are merely extrapolations of overall growth from a single flask after bi-daily dilutions of the cells. For example, the reference teaches that the cells were maintained at "a cell density of 0.5 x 10^6/ml" (see, e.g., WO 94/29436 page 27, lns. 7-9 generally; page 27, lns. 35-36 regarding Figure 1; page 28, lns. 30-32 regarding Figure 2; and page 29, lns. 13-18 regarding Figure 3). Furthermore, such extrapolation would result in the cells in volume of 100 liters or more at densities of 10^6 cells/ml, not the high densities required by the instant claims. Nowhere, does June *et al.* teach or suggest any cell densities in of 10^{10} cells per liter. Thus, June *et al.* does not teach or suggest growth of T cells under conditions that produce high cell densities in excess of 10^{10} cells/liter, to obtain clinically relevant numbers of cells, as required by the claims.

June *et al.* teaches a method can be for expanding T cells in long term tissue culture to obtain a population **increased in number** from about 100 to about 100,000 fold over the original starting cell population, **not increased in cell density** Thus, Figures 1-3 actually only show that the method results in cell numbers that *theoretically* could exceed 1 x 10^{10} cells, but in no way teaches or suggests preparation of such cells at a *density* of about 10^{10}/liter or more, as required by the claims. Furthermore, the resulting volume of 10^{10} cells if extrapolated from the figure, would be 100's of liters, which are not clinically relevant, since there is no way to introduce 100's of liters of any fluid into a mammal, particularly a human.

Moreover the teachings of the June *et al.* references, e.g., at page 9 first complete paragraph of June *et al.* '29436, do **not** suggest, mention or hint at a step that includes treatment of the T cells into Th1 cells during or prior to expansion to produce Th1 cells. In this paragraph, June *et al.* describes antigen specific activation of a population of cells to produce cells specific for a particular antigen; this is not the same as production populations of cells with high levels of Th1 cells or Th2 cells. Preparing antigen-specific cells does not involve differentiation of cells to produce Th1 cells as claimed in the instant claims. June *et al.* does not teach or suggest or mention any methods in which particular subsets of T cells are produced. In fact the data presented in June *et al.* (Table 2) demonstrates that the resulting cells are not Th1 or Th2 cells, but are Th0 cells. The resulting cytokine profile indicates that the cells of June *et al.* appear to be CD4+ cells of precursor Th0 phenotype. It can be seen that by the third cycle of stimulation in the June *et al.* experiment, the cells are producing IL-2, IFN-γ **AND** IL-4. Hence the resulting population of cells does not have characteristics of a population of Th1 cells, but rather has a mixed phenotype. These cells, which produce IL-4 are clearly not Th1 cells. Since they produce INF-γ, they cannot be Th2 cells. Hence there is no evidence that the June *et al.* produces Th1 cells, and June *et al.* certainly does not mention of suggest expansion of T cells to produce such subsets. June *et al.* admits that the expanded CD4+ cells had unstable cytokine profile (see page 31, lines 26-29).

Furthermore, June *et al.* does not suggest a method for virally purging any cells, and does not suggest a method in which CD4+ cells that are HIV- after activation are selected. June *et al.* teaches removing CD4+ and expanding them, but does not suggest selecting for virally purged cells nor for , expansion under conditions for differentiation into Th1 cells. June *et al.* teaches expansion of CD4+ cells and suggests:

> may also be necessary is to avoid infecting the T cells during long-term stimulation or it may desirable to render the T cells permanently resistant to HIV infection. There are a number of techniques by which T cells may be rendered either resistant to HIV infection or incapable of producing virus prior to restoring the T cells to the infected individual. For example, one or more anti-retroviral agents can be cultured with CD4.sup.+ T cells prior to expansion to inhibit HIV replication or viral production (e.g., drugs that target reverse transcriptase and/or other components of the viral machinery, see e.g., Chow et al. (1993) Nature 361, 650-653).
>
> Several methods can be used to genetically transduce T cells to produce molecules which inhibit HIV infection or replication. . . .

Thus, the only mention June *et al.* has regarding HIV+ cells is directed to methods for avoiding infection, not for methods for selection HIV-. June *et al.* does not suggest selecting the HIV- cells and expanding them, and does not suggest selecting CD4+ cells that are HIV- after activation.

Thus, June *et al.*, alone or in combination with O'Garra *et al.*, does not teach or suggest activation of CD4+ cells and selection of HIV- cells from among those cells and expansion of the HIV- cells; nor does June *et al.* in combination with O'Garra *et al.* teach or suggest expansion of HIV- cells to the high densities and numbers required by the claims. Further there is no suggestion in either reference for activation of cells under conditions that promote Th1 cell differentiation of any cells and subsequent expansion thereof.

Carew

Carew does not cure the deficiencies in O'Garra *et al.* and June *et al.* Carew is directed to an *in situ* method for removing pathogenic agents from body fluids. The body fluid is perfused into a mixing coil with paramagnetic beads that selectively bind to the pathogenic agent; and the beads are then separated from the fluid. In one embodiment, blood is treated to remove infected T-lymphocytes by continuously perfusing the blood through the mixing coil using a peristaltic pump. Hence the method of Carew involves *in situ* filtration of the blood of an individual. It has nothing to do with *in vitro*

expansion of cells or treatment of cells *in vitro* or immunotherapy. Carew provides no teaching or suggestion for selection HIV- cells from activated CD4+ cells, nor subsequent expansion thereof.

The method of Carew involves filtration of the blood of an individual *in situ*; it has nothing to do with purging cells *in vitro* for culture *in vitro* for adoptive immunotherapy. Carew does not teach or suggest use of its method in combination with adoptive immunotherapy protocols in which selected cells are first activated and then expanded. Carew does not suggest selecting CD4+ cells that are HIV- after activating the cells. Nor does Carew teach or suggest a step of expanding the Th1 cells to an excess of 10^{10} cells in a volume of a liter or less in the absence of IL-2. Thus, Carew does not cure the deficiencies in the teachings of O'Garra *et al.* and June *et al.*

Nabel *et al.*

Nabel *et al.* does not cure the deficiencies in the teachings of O'Garra *et al.*, June *et al.* and Carew. Nabel *et al.* teaches that human immunodeficiency virus (HIV) production from latently infected T lymphocytes can be induced with compounds that activate the cells to secrete lymphokines. Because Nabel *et al.* provides no teachings or suggestions directed to methods for preparing HIV- compositions of cells, Nabel *et al.* has no relevance to the instant claims, which are directed to methods for preparing compositions of virally purged cells.

Thus Nabel does not cure the deficiencies in the teachings of O'Garra and/or June *et al.* and Carew. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

The Examiner has failed to set forth a case of *prima facie* obviousness

(1) Relevant law

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. § 103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (*ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 329,

933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (BPAI 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)).

There would have been no motivation to have combined the teachings of O'Garra *et al.* with June *et al.*, Carew and Nabel, and the combination does not result in the instantly claimed methods

Motivation

O'Garra *et al.* describes properties of Th1 and Th2 cells *in vivo* and explains *in vivo* establishment of lymphokine-producing phenotypes and development thereof. As set forth above, O'Garra *et al.* does not teach or suggest preparation of populations of Th1 cells *in vitro*, but is studying T cells *in vivo*.

June *et al.* is directed to methods for expansion of cells. As discussed above, the cells produced by the method of June *et al.* are not predominantly Th1 cells. The cytokine profile of the resulting cells (Table 2) is clearly that of a mixed population.

Carew is directed to an *in situ* perfusion-based method of removing pathogens from body fluids, and Nabel *et al.* teaches that compounds that activate lymphocytes can induce production of HIV from latently infected cells. Thus, Nabel *et al.* is merely directed to an observation and is of no relevance to the instantly claimed methods.

Thus, the references are directed to diverse topics and studies; there would have been no motivation to have combined the teachings of these references. Notwithstanding this lack of motivation, as established above, such combination, does not result in the instantly claimed methods.

The combination of references does not result in the claimed subject matter

Notwithstanding the lack of motivation, even if combined, the combination of cited references do not teach, suggest or result in a method that includes steps of collecting leukocyte-containing material from an HIV^+ human; exposing the material to mitogenic monoclonal antibodies to induce *in vitro* cell proliferation sufficient for infusion into the mammal for use in an immunotherapy treatment, where the *in vitro* cell proliferation is produced without the use of exogenous Il-2; purging HIV + cells from $CD4^+$ cells in the material by selection of CD4 + antigen after activation, and are polyclonally activating and again selected for CD4 antigen; and producing excess of 10^{10} cells at a density of at least about 10^8 cells/ml. Furthermore, the combination of cited references does not teach or suggest activation of the cells occurs under conditions that promote Th1 cell differentiation to produce a population of cells that contains predominantly Th1 cells as required by the claims; nor a method for expansion of virally purged cells to densities of at least 10^8 cells/ml (claim 168).

None of the cited references, taken alone or in any combination thereof, teaches or suggests anything regarding selection of HIV- cells and preparation of high densities of cells as required by all of the instant claims, and none suggest preparation of **populations of clinically relevant numbers of cells that contain predominantly Th1 cells**. None of the cited references suggests any method that involves restoration of the immune system balance by administration of compositions containing substantially only one type of regulatory immune cell corresponding to Th1.

Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

Rebuttal to comments of the Examiner

The Examiner states that the ordinarily skilled artisan would have "prepared cells at any desired concentration" and to have "created the claimed invention" because O'Garra *et al.* teaches that Th1 cells can be produced, June *et al.* teaches methods of expanding cells, Carew teaches that HIV^+ cells can be removed from blood. The Examiner states that June *et al.* provides motivation because June *et al.* teaches "a variety of uses for expanded T cell subsets" and Carew teaches that "HIV infected T cells should be removed from blood product."

1. O'Garra *et al.* does not teach that Th1 cells can be produced *in vitro*. O'Garra *et al.* is directed to a study to assess whether they exist *in vivo*. There is no teaching or suggestion in O'Garra *et al.* for preparation of populations of Th1 cells *in vitro*.

2. A teaching a reference for filtering of blood *in situ* does not suggest a method for producing cells for adoptive immunotherapy in which HIV+ cells are selectively removed; and it does not suggest selecting CD4+ cells that are HIV- after activation.

3. June *et al.* does not teach a variety of uses of expanded T cell subsets. June *et al.* does not teach or suggest any method for preparing T cell subsets nor any method in which a T cell subset is prepared. The methods of June *et al.* are for expanding cells; there is no suggestion in June *et al.* for preparation of high densities of cells nor any suggestion to do so.

5. The comment that the ordinarily skilled artisan would have "prepared cells at any desired concentration" begs the question of obviousness. The combination of teachings of cited references must teach or suggest the density of cells that is claimed. The fact that an ordinarily skilled artisan would have prepared cells at desired concentration is not relevant to the issue of

obviousness; the references must teach or suggest the concentration (in this instance the amount and density) that is produced. None of the cited references, singly or in combination, teaches or suggests the instantly claimed amounts of cells and densities thereof.

Furthermore the instant claims are directed to methods, the combination of references must result in a method that includes all steps as claimed. The combination fails to suggest a method involving collection of cells from an HIV+ subject, activation and selective removal of HIV+ cells and expansion of the HIV+ cells to clinically relevant densities and amounts. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

The Rejection over O'Garra *et al.* in view of June *et al.*, Carew and Nabel *et al.* is Based on Improper Use of Hindsight.

The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. *In re Laskowski*, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

It appears that the Examiner has combined the teachings of the prior art with those of the instant application. Only the instant application teaches activation and the subsequent expansion of these cells to an amount in excess of 10^{10} cells in a volume of a liter or less; only the instant application teaches a method for activating and selectively removing HIV+ cells; and only the instant application teaches differentiation of mononuclear cells into predominantly Th1 cells *in vitro* for immunotherapy. Because the combination of cited prior art does not teach or suggest any of these claim requirements, for the rejection to

set forth a *prima facie* case of obviousness, it necessarily must have employed the teachings of the specification to make the combination.

Claims 37, 39 and 159-161

Claims 37, 39 and 159-161 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Seder *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A. 90*:10188-10192 in view June *et al.* (WO 94/29436) or June *et al.* (U.S. Patent No. 5,858,358 because the Examiner alleges that Seder *et al.* teaches that Th1 cells can be preodced by treating CD4+ cells with Il-2 or gamma-interferon, June *et al.* (PCT or US Patent) teaches methods of expanding T cells; and Carew teaches that HIV^+ cells can be removed from blood by treatment with immunoreactive beads coated with an HIV-binding reagent. The Examiner concludes that it that the ordinarily skilled artisan would have "prepared cells at any desired concentration" and to have "created the claimed invention" because Seder *et al.* teaches that Th1 cells can be produced, June *et al.* teaches methods of expanding cells, Carew teaches that HIV^+ cells can be removed from blood. The Examiner states that June *et al.* provides motivation because June *et al.* teaches "a variety of uses for expanded T cell subsets" and Carew teaches that "HIV infected T cells should be removed from blood product." This rejection is respectfully traversed.

Teachings of the cited references and differences from the instant claims

Seder *et al.*

Seder *et al.* teaches that naive $CD4^+$ T cells produce IL-2, but little or no IFN-γ, and states that *in vitro* they develop into producers of IL-4 or IFN-γ depending upon the conditions of the priming culture. Using TCR transgenic $CD4^+$ cells, Seder *et al.* presents studies that examine the role of IL-12 and IL-4 in antigen-specific priming. Seder *et al.* teaches that IL-12 enhances the ability of cells to develop in IFN-γ producers upon restimulation. Seder *et al.* concludes that Il-12 has a major effect on the inductive phase of T-cell priming by enhancing commitment to IFN-γ production. It is respectfully submitted that no

where does Seder *et al.* teach any information regarding Th1 cells, except to state that the results indicate that the cytokines present at the outset of a response powerfully determine the character of the ensuing response, suggesting that (page 10192):

> ...optimal vaccine strategies for protection against intracellular organisms might include both administration of IL-12 and neutralization of IL-4. **A major question that remains open** is whether established Th1 or Th2 phenotypes can be altered by manipulations of the cytokine environment.(emphasis added)

Therefore, the only information Seder *et al.* discloses regarding Th1 cells is the equivocal conclusion that **it is not clear** whether Th1 and Th2 phenotypes can be altered *in vivo*. Furthermore, Seder *et al.* contemplates alteration of the phenotypes *in vivo* not in *in vitro* nor in connection with methods of producing expanded cells for immunotherapy.

Thus, Seder *et al.* does not suggest production of compositions of predominantly Th1 cells, and certainly does not provide any motivation to produce high densities of Th1 cells in excess of 10^{10} cells/liter. Seder *et al.* when describing therapeutic protocols merely suggests a vaccine containing IL-12 and an IL-4 neutralizing agent, and suggest nothing about an *in vitro* method for production of high quantities and densities of virally-purged CD4+ cells. Therefore, Seder *et al.* is deficient in failing to teach or suggest any steps in the instantly claimed methods. Therefore, Seder *et al.* does not teach a method involving collecting mononuclear cells from a patient infected with HIV, activating the cells by contacting the cells with mitogenic antibodies, selecting CD4+ cells that are HIV- after activation, and then expanding the selected cells to clinically relevant numbers in excess of 10^{10} in the absence of interleukin-2 (IL-2). Further Seder *et al.* does not suggest directing differentiation *in vitro* of the cells during activation to produce Th1 cells.

Therefore, Seder *et al.* is deficient in failing to teach or suggest any steps in the instantly claimed methods.

Secondary references

The teachings of the secondary references are discussed above.

There would have been no motivation to have combined the teachings of Seder *et al.* with June *et al.*, Carew and Nabel and the combination does not result in the instantly claimed methods

Seder *et al.* is merely directed to assessing the role of cytokines in determining T-lymphocyte function and concludes that the ability to alter phenotype *in vivo* is unresolved. Seder *et al.* teaches or suggests nothing regarding preparation of clinically relevant numbers and densities of CD4+ HIV- cells from a cells from an HIV+ subject.

Seder *et al.* does not suggest preparing large quantities of T cells and nothing about large quantities of populations of Th1 cells nor therapeutic or other uses thereof. In fact, Seder *et al.* raises a doubt whether the phenotype of such cells can be altered *in vivo* and provides no teachings or suggestions regarding *in vitro* preparation. Since Seder *et al.* does not provide a reason to generate large quantities of T cells, provides no teachings or suggestions regarding methods for preparing cells *in vitro*, there would have been no motivation to have combined the teachings of Seder *et al.* with those of June *et al.* As discussed above, the teachings of Carew are directed to an *in situ* method of blood filtration; Carew does not teach or suggest selecting selecting CD4+ cells that are HIV- after activation; Carew does not mention any method in which cells are activated or selected.

There is nothing in the teachings of the secondary references and Seder *et al.* that would have motivated combination of their teachings. Seder *et al.* is a study of T cell priming to assess whether phenotype can be altered *in vivo*; June *et al.* is directed to methods for expansion of T cells *in vitro*, and Carew is directed to a method for filtration of blood *in situ*. These references are directed to different technologies, and hence would not have been combined by an

ordinarily skilled artisan. Furthermore, notwithstanding this, their combination does not result in the instantly claimed methods.

The combination of references does not result in the claimed methods

Seder *et al.* concludes that the ability to manipulate T cell phenotype is unclear, and does not provide a procedure for doing so. Seder does not teach or suggest methods for producing compositions containing predominantly Th1 cells of any T-cell subset population, including $CD4^+$ cells can be produced. Moreover, Seder *et al.* does not contemplate any therapeutic methods that requires administration of cells. Seder *et al.* does not contemplate alteration of immune balance *in vivo* by administration of large quantities of one type of T cell. Seder *et al.* does not teach or suggest a method for producing virally purged CD4+ cells. As discussed above, neither June *et al.* nor Carew does not teach or suggest selecting selecting CD4+ cells that are HIV- after activation.

None of the secondary references teaches or suggests involving removal of cells from an HIV+ subject, activating and selecting HIV- cells and expanding the cells to an amount of cells in excess of 10^{10} cells in a volume of a liter or less. Furthermore, none of the references, singly or in any combination thereof, suggests activation of the cells *in vitro* under conditions in which the cells become Th1 cells.

Accordingly, the combination of cited references do not teach, suggest or result a method including the steps of collecting mononuclear cells or any cells from a patient infected with HIV; contacting the cells with mitogenic antibodies to induce cell activation, selecting CD4+ cells that are HIV- after activation; and inducing cell proliferation and expanding the selected cells to an excess of 1×10^{10} cells, where the cells are contained in a volume of a liter or less and cell proliferation and expansion is performed in the absence of exogenous interleukin-2 (IL-2). Furthermore, the combination of teachings does not teach or suggest, activating of the cells occurs under conditions that promote Th1 cell

differentiation to produce a population of cells that contains predominantly Th1 cells. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

The Rejection over Seder *et al.* in view of June *et al.*, Carew is Based on Improper Use of Hindsight.

It is respectfully submitted that the Examiner has combined the teachings of the prior art with those of the instant application. Only the instant application that teaches a method for producing clinically relevant numbers and densities of virally purged CD4+ cells by collecting mononuclear cells from a patient infected with HIV; contacting the cells with mitogenic antibodies to induce cell activation, **selecting CD4+ cells that are HIV- after activation;** and inducing cell proliferation and expanding the selected cells to an excess of 1 x 10^{10} cells in a volume of less and a liter and in the absence of exogenous interleukin-2. Further none of the cited references activation of the cells occurs conditions that promote Th1 cell differentiation to produce a population of cells that contains predominantly Th1 cells. It is the instant application that teaches and shows that it is possible to selectively expand Th1 cells to clinically relevant numbers and it is the instant application that provides the motivation to do so. None of the cited references suggests a therapeutic approach in which compositions of predominantly Th1 cells are prepared in the amounts and densities claimed.

Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

REJECTION OF CLAIMS 165 and 167 UNDER 35 U.S.C. § 103(a)

Claims 165 and 167 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over O'Garra *et al.* in view June *et al.* (WO 94/29436 or U.S. Patent No. 5,858,358) and Carew and Nabel *et al.* as applied to claims 37, 39,

159-161 above, and further in view of Cracauer *et al.* (U.S. Patent No. 4,804,628). This rejection is respectfully traversed.

The Claims

Claims 165 and 167 are directed to method claims 37 and 39, respectively, where cell expansion is effected in a hollow fiber reactor.

Teachings of the cited references and differences from the instant claims

As set forth above, combination of O'garra *et al.*, June *et al.*, Carew and Nabel does not teach or suggest a method for production of CD4+ virally-purged cells in an amount greater than 10^{10} cells in a volume of a liter or less, nor a method in which CD4+ cells that are HIV- are selected after activation. The combination of cited references does not suggest selective expansion of Th1 cells.

Cracauer *et al.*

Cracauer *et al.* teaches a hollow fiber cell culture device that includes a hollow fiber cartridge having a shell and a plurality of capillaries extending through the shell with at least some capillaries having semi-permeable walls. A cell culturing space is located between the shell and the capillaries. The device includes a chamber containing a second medium supply fluidly connected to the cell culturing space.

Cracauer *et al.* does not teach or suggest use of its hollow fiber cell culture for growing clinically relevant numbers of any type of lymphoid cell, much less Th1 cells, as required in Applicant's claims. The device of Cracauer *et al.* is not taught to be suitable for growing lymphoid cells at densities exceeding 1 x 10^{10} cells/liter.

The Examiner has failed to set forth a case of *prima facie* obviousness

The combination of references does not result in the claimed subject matter

As discussed above, the combination of O'Garra *et al.*, June *et al.*, Carew and Nabel fails to teach or suggest the instantly claims methods. Cracauer *et al.* does not cure this deficiency. Cracauer *et al.* teaches a hollow fiber device. There is no teaching or suggestion in Cracauer *et al.* to use the device for expanding T cells at high cell density nor how to adapt the device to achieve such a goal. Therefore, Cracauer does not cure the deficiencies in the teachings of O'Garra *et al.*, June *et al.* and Carew, and the combination of references does not teach or suggest the instantly claimed methods. **CLAIMS 165 and 167**

Claims 165 and 167 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Seder *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A. 90*:10188-10192 in view June *et al.* (WO 94/29436 or U.S. Patent No. 5,858,358) and Carew as applied to claims 37, 39, 159-161 above, and further in view of Cracauer *et al.* (U.S. Patent No. 4,804,628) because . This rejection is respectfully traversed.

The Claims

Claims 165 and 167 are directed to method claims 37 and 39, respectively, where cell expansion is effected in a hollow fiber reactor.

Teachings of the cited references and differences from the instant claims

As set forth above, the combination of Seder *et al.*, June *et al.*, Carew does not teach or suggest the instantly claimed methods. Cracauer *et al.* does not cure this deficiency.

The Examiner has failed to set forth a case of *prima facie* obviousness

The combination of references does not result in the claimed methods

As discussed above, the combination of Seder *et al.*, June *et al.* and does not result in the instantly claimed methods. Cracauer *et al.* does not cure the deficiencies in the teachings of the primary references because Cracauer *et al.*

teaches a hollow fiber device. There is no teaching or suggestion in Cracauer *et al.* to use the device for expanding T cells at high cell density nor how to adapt the device to achieve such a goal. Further, Cracauer *et al.* does not teach or suggest a method for selecting CD4+ cells that are HIV- after activation. Cracauer *et al.* does not teach or suggest expanding Th1 cells. Therefore, Cracauer does not cure the deficiencies in the teachings of Seder *et al.*, June *et al.* and Carew.

* * *

In view of the above remarks and the amendments and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: MICHEAL L. GRUENBERG

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Kelly Fischer

MARKED UP CLAIMS (37 C.F.R. § 1.121)

Please cancel claims 36, 155, 156, 157, 158, 159 and 162.

Please amend claims 37, 38, 39 and 154, as follows:

37. (Three Times Amended) [The method of claim 36] A method of producing virally purged CD4+ cells, comprising:

(a) collecting mononuclear cells from a patient infected with HIV;

(b) contacting the cells with mitogenic antibodies to induce cell activation,

wherein, in the contacting step, the activation of the cells occurs under conditions that promote Th1 cell differentiation to produce a population of cells that contains predominantly Th1 cells;

(c) selecting CD4+ cells that are HIV- after activation; and

(d) inducing cell proliferation and expanding the selected cells to an excess of 1 x 10^{10} cells, wherein:

cell proliferation and expansion is performed in the absence of exogenous interleukin-2 (IL-2); and the cells are contained in a volume of a liter or less.

38. (Three Times Amended) The method of claim [36] 37, further comprising:

after selecting CD4+ cells that are HIV- and prior to expanding the selected cells, growing a plurality of aliquots in the presence of mitogenic agents;

selecting from the aliquots those that are HIV-; and

then expanding the selected cells to [in] an excess of 1 x 10^{10} cells per liter.

39. (Twice Amended) The method of claim [36] 37, wherein the cells are activated with anti-CD3 monoclonal antibodies in the presence of interferon-γ (IFN-γ).

154. (Amended) The method of claim [36] 40, wherein cell expansion is effected in a hollow fiber bioreactor.